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Brief Clinical Report

Skeletal and Cardiac Malformations With Thrombocytopenia: A New Syndrome?

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We describe a female patient with multiple anomalies suggestive of a new syndrome. Manifestations include: VSD and ASD, mild developmental delay, conductive hearing loss, minor facial anomalies, thrombocytopenia, and radiological findings (including carpal fusion). Some of these manifestations may be present in the Keutel syndrome, IVIC syndrome, and the 10qter deletion syndrome. However, none of these syndromes can explain the spectrum of anomalies seen in our patient.

KEY WORDS: thrombocytopenia, skeletal malformations, cardiac malformations

INTRODUCTION

The patient presented invites nosologic attention and suggests the presence of a previously undescribed condition.

CLINICAL REPORT

The patient (A.P.) is the 8-year-old daughter of a nonconsanguineous couple of Italian descent. An older sister is healthy. The pregnancy was complicated by symptoms of peptic ulcer, aggravated by the pregnancy, and late toxemia. There is no history of exposure to teratogens. A.P. was born at 35 weeks of gestation by cesarean section because of fetal distress. Her mother was 38 years old and her father was 32 at the time of delivery.

At 3 weeks, she was noted to have minor anomalies and thrombocytopenia. Her platelet count has generally remained between 15 and 70 $\times$ 10^9/L (normal values 140–450 $\times$ 10^9/L). There was little response to therapy with either intravenous immune globulin or prednisone. However, she had an excellent response to a platelet transfusion of four units, with an increase in her platelet count from 50 $\times$ 10^9/L to 147 $\times$ 10^9/L. Two days later, her count remained 126 $\times$ 10^9/L. Two bone marrow aspirations, at age 21 months and at 5 9/12 years, demonstrated abnormal megakaryocytes, with small bi- and trinucleated forms along with abnormal myeloid segmentation.

As an infant, a grade III/VI systolic murmur was noted. At 5 months, cardiac catheterization demonstrated a large ventricular septal defect and a secundum atrial septal defect; these were corrected surgically.

There was mild developmental delay. A.P. sat at 8 months, walked at 13 months, and spoke single words at 18 months.

Physical Examination

At the age of 7 9/12 years, height was 126 cm (50th centile) and OFC was 48 cm (<5th centile) (Fig. 1a,b). She had an unusual face characterized by hypertelorism, slightly simple convolutions of the pinnae, stenotic ear canals, small tympanic membranes, a prominent nose, and prognathism (Fig. 2a,b). The face was asymmetric. There was pallor around the optic disc of the right eye. The palate was high arched and the teeth were widely spaced. A grade IV systolic heart murmur was heard. There was an increased carrying angle of the upper limbs bilaterally. She also had bilateral single palmar creases, tapering fingers, partial dermal syndactyly of the midproximal phalanx, particularly of the 4th and 5th fingers, fusiform index fingers, and single interphalangeal creases of her 4th and 5th fingers bilaterally (Fig. 3a,b). Fine motor movements were mildly decreased bilaterally; attention span was also decreased.

Investigations

Radiological examination of the hands and wrists demonstrated bilateral carpal coalition (capitate-hamate fusion), tapering distal phalanges, and partial soft tissue syndactyly at the finger bases, more evident

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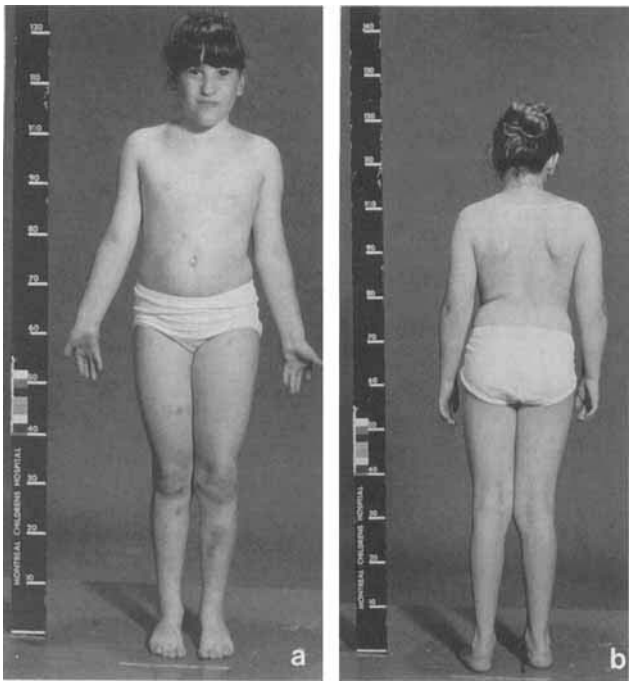

Fig. 1. **(a)** Frontal view of total body. Note increased carrying angle and asymmetry. **(b)** Dorsal view of total body. Note asymmetry.

between the 4th and 5th fingers of both hands (Fig. 4). There was also bilateral coxa valga (Fig. 5), bone expansion of the pubic and ischial regions with a wide puboischial synchondrosis, evidence for fusion between the anterior arches of C1 vertebra, and C2 vertebral body (Fig. 6). A computed tomographic scan of the head documented slight asymmetry of the lateral ventricles. An audiology examination demonstrated bilateral mild to moderate conductive hearing loss. A blood karyotype with 400–600 band resolution was normal (46,XX). Fluorescence in situ hybridization (FISH) studies were performed using the probe D22S75 (ONCOR) mapping to the DiGeorge syndrome (DGS) region. These studies failed to detect a deletion. Mild deficiency in intellectual function with a delay of approximately 1 year was shown in psychological testing at age 7 years.

DISCUSSION

Our patient presented with an unusual combination of minor anomalies, VSD and ASD, radiological anomalies, and chronic thrombocytopenia. The radiological anomalies consisted of carpal fusion and C1-C2 vertebral assimilation. Fusion of carpal bones is rare and may be an isolated anomaly. It is most common between the lunate and triquetrum or capitate and hamate bones, but fusions have been described in almost every combination. Carpal coalition is also seen in the fetal alcohol syndrome, in arthrogryposis and in other skeletal dysplasias.

The thrombocytopenia seen in our patient is possibly a result of production failure rather than excessive platelet destruction due to the fact that platelet counts remained elevated 2 days following a platelet transfusion in addition to the presence of abnormal megakaryocytes.

Some of the manifestations of our patient are also seen in DiGeorge syndrome (DGS). These characteristics in common include hypertelorism, ear anomalies, VSD, and mild mental retardation. FISH studies did not show a deletion in the 22q11 (DGS) region [Driscoll et al., 1992].

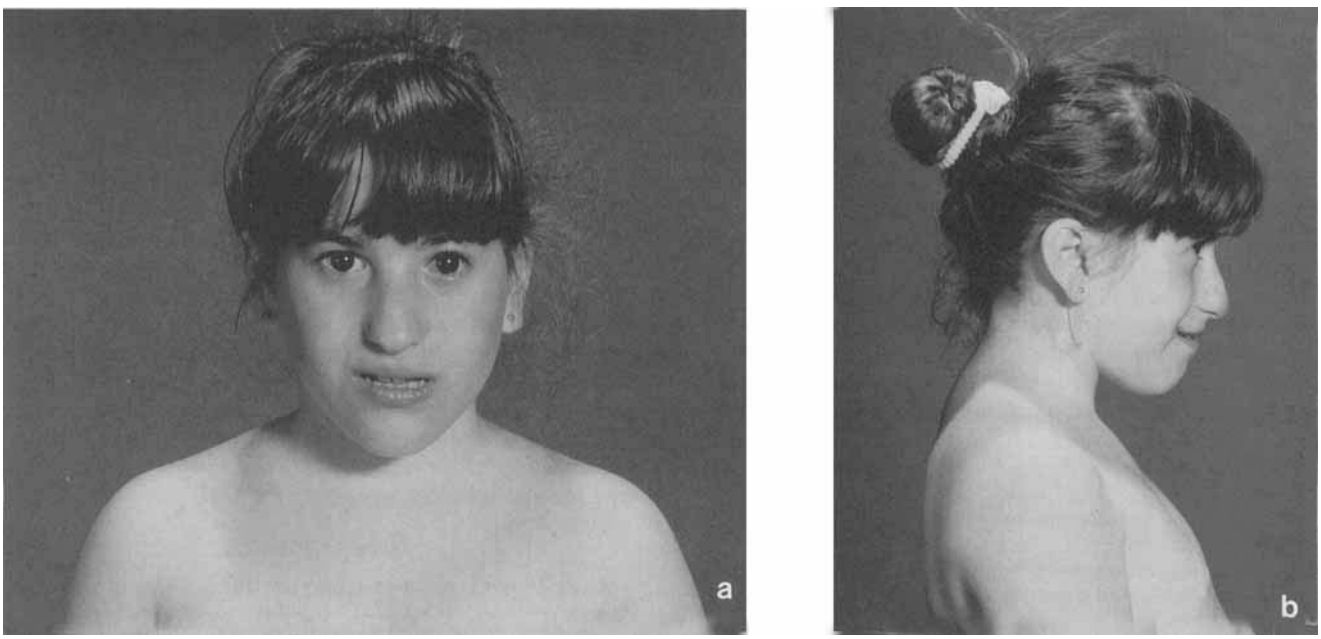

Fig. 2. **(a)** Face. Note asymmetry. **(b)** Profile.

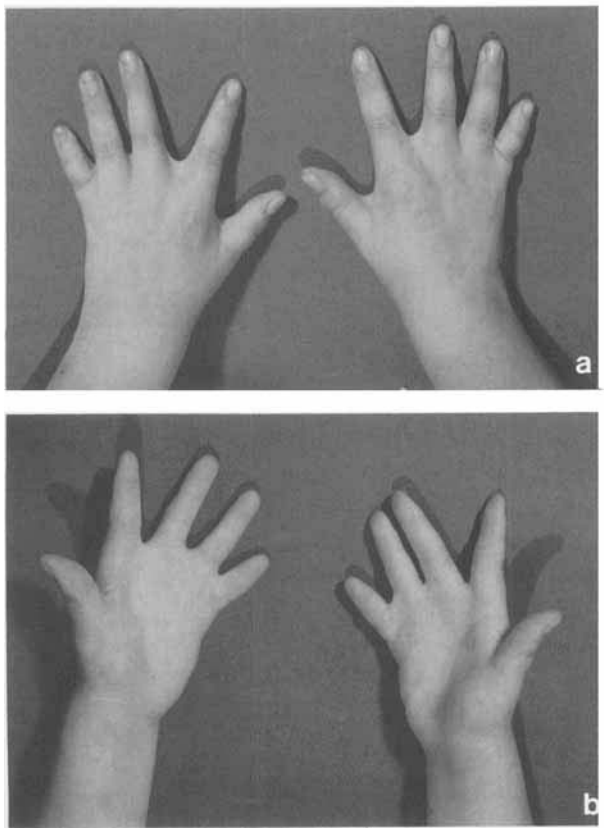

Fig. 3. **(a)** Dorsa of hands. Note interdigital webbing and brachydactyly. **(b)** Palmar view of hands. Note brachydactyly and tapering fingers.

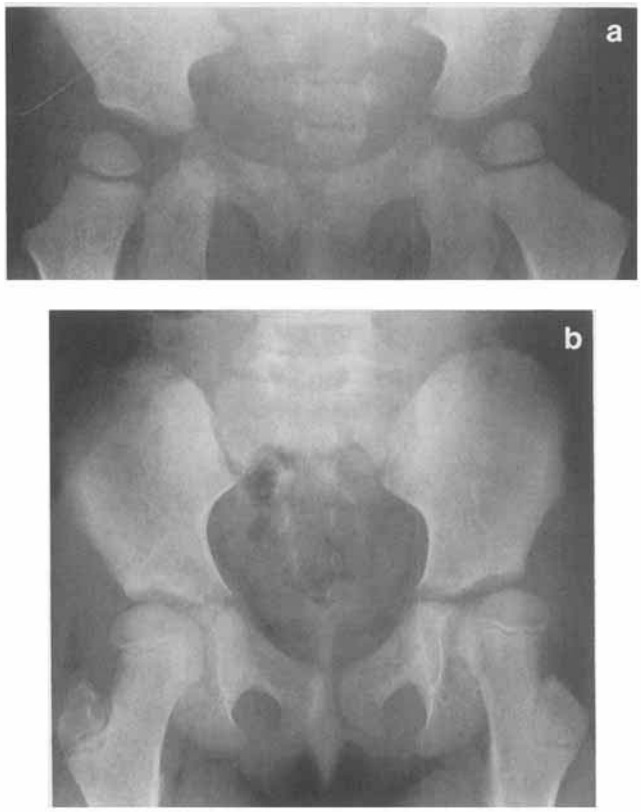

Fig. 5. Anteroposterior view of the pelvis and hip. **(a)** At age 2 years and **(b)** at age 8 years showing bilateral progressive coxa valga with uncovering of the outer part of the femoral heads as well as expansion of the pubic and ischial bones with a wide puboischial synchondrosis.

A syndrome defined by a 10qter deletion has among its manifestations congenital heart defects and thrombocytopenia [Gorinati et al., 1989]. In addition, it may present with conductive hearing loss, microcephaly, mild mental retardation and hypertelorism, short neck, syndactyly of the fingers, and single palmar creases [Gorinati et al., 1989; Wulfsberg et al., 1989; Borovik and Brunoni, 1991]. These anomalies are also seen in A.P. Approximately 55% of reported cases had urogenital anomalies that are not present in our patient. Moreover, her radiological findings have not been reported in cases with chromosome 10qter deletion syndrome. Most individuals with chromosome 10qter deletion syndrome have breakpoints in the 10q25 or 10q26 region [Wulfsberg et al., 1989; Borovik and Brunoni, 1991], whereas others have their breakpoints at 10q23 [Gorinati et al., 1989]. Even though no chromosomal anomalies were detected in our patient with prophase banding, it is possible that there is a submicroscopic deletion in the 10q23–10qter region resulting in her clinical manifestations. FISH studies will therefore be performed.

Fig. 4. Posteroanterior view of both hands and wrists showing bilateral capitate-hamate fusion (carpal coalition), tapering of the tips of the distal phalanges as well as partial soft tissue syndactyly at the finger bases of both hands, more extensive between the 4th and 5th fingers.

IVIC syndrome, also known as Oculo-oto-radial syndrome, is an autosomal dominant disorder involving developmental defects of the upper limbs [Arias et al., 1980]. A constant finding of IVIC syndrome is radial ray defects, which are variably expressed and sometimes manifested as carpal fusion [Arias et al., 1980]. Thrombocytopenia, conductive hearing loss, and carpal fusion (also characteristic of IVIC syndrome) [Arias et al., 1980; Sammito et al., 1988; Czeizel et al., 1989], are seen in our patient. However, she does not have strabismus, which is usually seen in IVIC syndrome, nor

Fig. 6. Lateral view of the cervical spine demonstrates fusion between the anterior arch of C1 and the body of C2. The overall normal cervical lordosis is well preserved.

leukocytosis, which affects many of these patients. Furthermore, there have been no reported cases of IVIC syndrome with congenital heart malformations.

Keutel et al. [1971] described a brother and sister with metacarpal fusion, VSD and ASD in a new autosomal recessive malformation syndrome, which now bears Keutel's name. The present case has several of the characteristics reported in Keutel syndrome, notably carpal fusion, cardiac defects, conductive hearing loss, borderline mental retardation, hypertelorism, brachytelephalangy, and syndactyly of the fingers [Fryns et al., 1984; Cormode et al., 1986; Khosroshahi et al., 1989; Ziereisen et al., 1993]. However, the patient does not present with abnormal ossification or calcification of the cartilage, a feature found in all reported cases of Keutel syndrome [Ziereisen et al., 1993]. Furthermore, all previously reported patients had normal hematological status [Fryns et al., 1984; Khosroshahi et al., 1989].

TABLE I. Findings in 10qter, IVIC, and Keutel Syndromes

Findings	10qter	IVIC	Keutel	A.P.
Microcephaly	+	–	?	+
Hypertelorism	+	?	+	+
Congenital heart defect	+	–	+	+
Thrombocytopenia	+	+	–	+
Carpal fusion	–	+	+	+
Tapering distal phalanges	–	?	?	+
Syndactyly	+	?	+	+
Hearing loss	+	+	+	+
Mild mental retardation	+	?	+	+

The combination of anomalies found in this patient does not, to our knowledge, correspond to a previously described syndrome. We therefore propose this to be a new condition of either a genetic or environmental cause.

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